

PATENT COOPERATION TREATY

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From the INTERNATIONAL SEARCHING AUTHORITY

PCT

To:
WOLF, GREENFIELD & SACKS, P.C.
600 Atlantic Avenue
Federal Reserve Plaza
Boston, Massachusetts 02210
UNITED STATES OF AMERICA

NOTIFICATION OF TRANSMITTAL OF
THE INTERNATIONAL SEARCH REPORT
OR THE DECLARATION

(PCT Rule 44.1)

Applicant's or agent's file reference 10277/7004W0	Date of mailing (day/month/year) 03/12/1999
International application No. PCT/US 99/ 06874	International filing date (day/month/year) 30/03/1999
Applicant UNIVERSITY OF VERMONT	

DOCKETED
DEC 16 1999

1. ☒ The applicant is hereby notified that the International Search Report has been established and is transmitted herewith.

Filing of amendments and statement under Article 19:

The applicant is entitled, if he so wishes, to amend the claims of the International Application (see Rule 46):

When? The time limit for filing such amendments is normally 2 months from the date of transmittal of the International Search Report; however, for more details, see the notes on the accompanying sheet.

Where? Directly to the International Bureau of WIPO
 34, chemin des Colombettes
 1211 Geneva 20, Switzerland
 Facsimile No.: (41-22) 740.14.35

For more detailed instructions, see the notes on the accompanying sheet. *

Initials
ECB
Docket Entry 2-3-00
Docket Cross Off
Order Copies (2)
Annuities
Confirmation

2. ☐ The applicant is hereby notified that no International Search Report will be established and that the declaration under Article 17(2)(a) to that effect is transmitted herewith.

3. ☐ With regard to the protest against payment of (an) additional fee(s) under Rule 40.2, the applicant is notified that:

☐ the protest together with the decision thereon has been transmitted to the International Bureau together with the applicant's request to forward the texts of both the protest and the decision thereon to the designated Offices.

☐ no decision has been made yet on the protest; the applicant will be notified as soon as a decision is made.

4. **Further action(s):** The applicant is reminded of the following:

Shortly after **18 months** from the priority date, the international application will be published by the International Bureau. If the applicant wishes to avoid or postpone publication, a notice of withdrawal of the international application, or of the priority claim, must reach the International Bureau as provided in Rules 90bis.1 and 90bis.3, respectively, before the completion of the technical preparations for international publication.

Within **19 months** from the priority date, a demand for international preliminary examination must be filed if the applicant wishes to postpone the entry into the national phase until 30 months from the priority date (in some Offices even later).

Within **20 months** from the priority date, the applicant must perform the prescribed acts for entry into the national phase before all designated Offices which have not been elected in the demand or in a later election within 19 months from the priority date or could not be elected because they are not bound by Chapter II.

Name and mailing address of the International Searching Authority European Patent Office, P.B. 5818 Patentlaan 2 NL-2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl. Fax: (+31-70) 340-3016	Authorized officer Barbara Klaver
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NOTES TO FORM PCT/ISA/220

These Notes are intended to give the basic instructions concerning the filing of amendments under article 19. The Notes are based on the requirements of the Patent Cooperation Treaty, the Regulations and the Administrative Instructions under that Treaty. In case of discrepancy between these Notes and those requirements, the latter are applicable. For more detailed information, see also the PCT Applicant's Guide, a publication of WIPO.

In these Notes, "Article", "Rule", and "Section" refer to the provisions of the PCT, the PCT Regulations and the PCT Administrative Instructions respectively.

INSTRUCTIONS CONCERNING AMENDMENTS UNDER ARTICLE 19

The applicant has, after having received the international search report, one opportunity to amend the claims of the international application. It should however be emphasized that, since all parts of the international application (claims, description and drawings) may be amended during the international preliminary examination procedure, there is usually no need to file amendments of the claims under Article 19 except where, e.g. the applicant wants the latter to be published for the purposes of provisional protection or has another reason for amending the claims before international publication. Furthermore, it should be emphasized that provisional protection is available in some States only.

What parts of the international application may be amended?

Under Article 19, only the claims may be amended.

During the international phase, the claims may also be amended (or further amended) under Article 34 before the International Preliminary Examining Authority. The description and drawings may only be amended under Article 34 before the International Examining Authority.

Upon entry into the national phase, all parts of the international application may be amended under Article 28 or, where applicable, Article 41.

When?

Within 2 months from the date of transmittal of the international search report or 16 months from the priority date, whichever time limit expires later. It should be noted, however, that the amendments will be considered as having been received on time if they are received by the International Bureau after the expiration of the applicable time limit but before the completion of the technical preparations for international publication (Rule 46.1).

Where not to file the amendments?

The amendments may only be filed with the International Bureau and not with the receiving Office or the International Searching Authority (Rule 46.2).

Where a demand for international preliminary examination has been/is filed, see below.

How?

Either by cancelling one or more entire claims, by adding one or more new claims or by amending the text of one or more of the claims as filed.

A replacement sheet must be submitted for each sheet of the claims which, on account of an amendment or amendments, differs from the sheet originally filed.

All the claims appearing on a replacement sheet must be numbered in Arabic numerals. Where a claim is cancelled, no renumbering of the other claims is required. In all cases where claims are renumbered, they must be renumbered consecutively (Administrative Instructions, Section 205(b)).

The amendments must be made in the language in which the international application is to be published.

What documents must/may accompany the amendments?

Letter (Section 205(b)):

The amendments must be submitted with a letter.

The letter will not be published with the international application and the amended claims. It should not be confused with the "Statement under Article 19(1)" (see below, under "Statement under Article 19(1)").

The letter must be in English or French, at the choice of the applicant. However, if the language of the international application is English, the letter must be in English; if the language of the international application is French, the letter must be in French.

NOTES TO FORM PCT/ISA/220 (continued)

The letter must indicate the differences between the claims as filed and the claims as amended. It must, in particular, indicate, in connection with each claim appearing in the international application (it being understood that identical indications concerning several claims may be grouped), whether

- (i) the claim is unchanged;
- (ii) the claim is cancelled;
- (iii) the claim is new;
- (iv) the claim replaces one or more claims as filed;
- (v) the claim is the result of the division of a claim as filed.

The following examples illustrate the manner in which amendments must be explained in the accompanying letter:

1. [Where originally there were 48 claims and after amendment of some claims there are 51]:
"Claims 1 to 29, 31, 32, 34, 35, 37 to 48 replaced by amended claims bearing the same numbers; claims 30, 33 and 36 unchanged; new claims 49 to 51 added."
2. [Where originally there were 15 claims and after amendment of all claims there are 11]:
"Claims 1 to 15 replaced by amended claims 1 to 11."
3. [Where originally there were 14 claims and the amendments consist in cancelling some claims and in adding new claims]:
"Claims 1 to 6 and 14 unchanged; claims 7 to 13 cancelled; new claims 15, 16 and 17 added." or
"Claims 7 to 13 cancelled; new claims 15, 16 and 17 added; all other claims unchanged."
4. [Where various kinds of amendments are made]:
"Claims 1-10 unchanged; claims 11 to 13, 18 and 19 cancelled; claims 14, 15 and 16 replaced by amended claim 14; claim 17 subdivided into amended claims 15, 16 and 17; new claims 20 and 21 added."

"Statement under article 19(1)" (Rule 46.4)

The amendments may be accompanied by a statement explaining the amendments and indicating any impact that such amendments might have on the description and the drawings (which cannot be amended under Article 19(1)).

The statement will be published with the international application and the amended claims.

It must be in the language in which the international application is to be published.

It must be brief, not exceeding 500 words if in English or if translated into English.

It should not be confused with and does not replace the letter indicating the differences between the claims as filed and as amended. It must be filed on a separate sheet and must be identified as such by a heading, preferably by using the words "Statement under Article 19(1)."

It may not contain any disparaging comments on the international search report or the relevance of citations contained in that report. Reference to citations, relevant to a given claim, contained in the international search report may be made only in connection with an amendment of that claim.

Consequence if a demand for international preliminary examination has already been filed

If, at the time of filing any amendments under Article 19, a demand for international preliminary examination has already been submitted, the applicant must preferably, at the same time of filing the amendments with the International Bureau, also file a copy of such amendments with the International Preliminary Examining Authority (see Rule 62.2(a), first sentence).

Consequence with regard to translation of the international application for entry into the national phase

The applicant's attention is drawn to the fact that, where upon entry into the national phase, a translation of the claims as amended under Article 19 may have to be furnished to the designated/elected Offices, instead of, or in addition to, the translation of the claims as filed.

For further details on the requirements of each designated/elected Office, see Volume II of the PCT Applicant's Guide.

PATENT COOPERATION TREATY

PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference 10277/7004W0	FOR FURTHER ACTION see Notification of Transmittal of International Search Report (Form PCT/ISA/220) as well as, where applicable, item 5 below.	
International application No. PCT/US 99/ 06874	International filing date (day/month/year) 30/03/1999	(Earliest) Priority Date (day/month/year) 17/04/1998
Applicant UNIVERSITY OF VERMONT		

This International Search Report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This International Search Report consists of a total of 7 sheets.
☒ It is also accompanied by a copy of each prior art document cited in this report.

1. Basis of the report

- a. With regard to the **language**, the international search was carried out on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.
- ☐ the international search was carried out on the basis of a translation of the international application furnished to this Authority (Rule 23.1(b)).
- b. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international search was carried out on the basis of the sequence listing :
- ☒ contained in the international application in written form.
- ☒ filed together with the international application in computer readable form.
- ☐ furnished subsequently to this Authority in written form.
- ☐ furnished subsequently to this Authority in computer readable form.
- ☐ the statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
- ☐ the statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished

2. ☒ **Certain claims were found unsearchable** (See Box I).

3. ☐ **Unity of invention is lacking** (see Box II).

4. With regard to the title,

- ☒ the text is approved as submitted by the applicant.
- ☐ the text has been established by this Authority to read as follows:

5. With regard to the abstract,

- ☒ the text is approved as submitted by the applicant.
- ☐ the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box III. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority.

6. The figure of the **drawings** to be published with the abstract is Figure No.

- ☒ as suggested by the applicant.
- ☐ because the applicant failed to suggest a figure.
- ☐ because this figure better characterizes the invention.

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☐ None of the figures.

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US 99/06874

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

see FURTHER INFORMATION sheet PCT/ISA/210
2. ☒ Claims Nos.: 50, 51, 57, 58, 84-137
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

see FURTHER INFORMATION sheet PCT/ISA/210
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.1

Although claims 1-3,5-9,13-16,18-20,23-26,29-34,38-39,42-49,53-56,139-142 (partially) 4,10-12,17,21,22,27,28,35-37,40,52,138 (completely) are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

Continuation of Box I.2

Claims Nos.: 50,51,57,58,84-137

A plurality of claims relate to methods/products defined by reference to a number of desirable characteristics or properties, namely

- 1) inducing agent effective to induce expression of MHC class II HLA-DR, HLA DP/DQ, Fas on the surface of mammalian cell
- 2) inducing agent effective to induce expression of B7 on the surface of the nerve cell
- 3) inducing agent effective to induce expression of CD28 in the surface of a neural activating cell
- 4) metabolic modifying/inhibiting agent, effective to increase/decrease the mitochondrial membrane potential
- 5) apoptotic chemotherapeutic agent
- 6) induce expression of a receptor for nerve growth factor
- 7) neural activating cell which induce neuronal differentiation in implanted B7 expressing neuron.

The claims cover all products/methods having these characteristics or properties, whereas the application provides support within the meaning of Article 6 PCT and/or disclosure within the meaning of Article 5 PCT for only a very limited number of such products/methods. In the present case, the claims so lack support, and the application so lacks disclosure, that a meaningful search over the whole of the claimed scope is impossible.

Independent of the above reasoning, the claims also lack clarity (Article 6 PCT). An attempt is made to define the product/method by reference to a result to be achieved. Again, this lack of clarity in the present case is such as to render a meaningful search over the whole of the claimed scope impossible. Consequently, the search has been carried out for those parts of the claims which appear to be clear, supported and disclosed, namely those parts relating to the products/methods comprising

- 1) administering an MHC class II HLA-DR or HLA-DP/DQ or Fas or B7 ligand, to selectively engage said molecules and decrease/increase mitochondrial membrane potential in the cell
- 2) method to induce the expression of immune recognition molecules (wherein by immune recognition molecules is meant MHC class II and B7) with a metabolic inhibition agent (fatty acid) to decrease the mitochondrial membrane potential and induce expression of said immune recognition molecules on the cell surface
- 3) adriamycin, gamma interferon, and staurosporin as inducing agent
- 4) sodium acetate as metabolic modifying agent (example 12)
- 5) method to kill cells contacting said cells with a UCP anti-sense nucleic acid.

The claims related to said above mentioned products/methods namely: 1,2,5,6,8,14,15,17,19,20,22,23,24,31,39-43,49,53,55,56,140, have been searched completely. All other claims, if not mentioned as not searched

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

claims, have been searched partially and in the light of the above mentioned searched subjects.

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

INTERNATIONAL SEARCH REPORT

International Application No

PCT/US 99/06874

A. CLASSIFICATION OF SUBJECT MATTER

IPC 6 A61K39/395 A61K38/21 A61K31/70 A61K38/17 A61K31/20
 A61K31/55 A61K31/505 A61K35/00 A61K38/00 G01N33/574
 C12N15/11

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 6 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	<p>DATABASE MEDLINE 'Online! US NATIONAL LIBRARY OF MEDICINE (NLM), BETHESDA, MD, US STREET D ET AL: "Interferon-gamma enhances susceptibility of cervical cancer cells to lysis by tumor-specific cytotoxic T cells." retrieved from STN Database accession no. 97302905 XP002122832 abstract & GYNECOLOGIC ONCOLOGY, (1997 MAY) 65 (2) 265-72. ,</p> <p style="text-align: center;">--- -/--</p>	<p>18,19, 24,79, 80,82</p>

☒ Further documents are listed in the continuation of box C.☒ Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search

18 November 1999

Date of mailing of the international search report

03/12/1999

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2
 NL - 2280 HV Rijswijk
 Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,
 Fax: (+31-70) 340-3016

Authorized officer

Covone, M

INTERNATIONAL SEARCH REPORT

International Application No

PCT/US 99/06874

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT		
Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	<p>SCAFFIDI C ET AL: "Two CD95 (APO - 1 / Fas) signaling pathways." EMBO JOURNAL, (1998 MAR 16) 17 (6) 1675-87. , XP002122827 abstract page 1676, right-hand column, paragraph 3 -page 1677, right-hand column, paragraph 1 page 1685, left-hand column, paragraphs 1,2 figure 3</p> <p style="text-align: center;">---</p>	<p>49, 53-56, 140</p>
A	<p>SUMMERFIELD A ET AL: "Lymphocyte apoptosis during classical swine fever: implication of activation-induced cell death." JOURNAL OF VIROLOGY, (1998 MAR) 72 (3) 1853-61. , XP002122828 page 1857, right-hand column, paragraph 2 -page 1858, left-hand column, paragraph 2 page 1858, right-hand column, paragraph 1 page 1859, right-hand column figure 8C</p> <p style="text-align: center;">---</p>	<p>49, 53-56, 140</p>
A	<p>LEE J W ET AL: "HLA-DR-mediated signals for hematopoiesis and induction of apoptosis involve but are not limited to a nitric oxide pathway." BLOOD, (1997 JUL 1) 90 (1) 217-25. , XP002122829 abstract page 217, left-hand column, paragraph 2 -right-hand column, paragraph 1</p> <p style="text-align: center;">---</p>	<p>1-12, 18-20, 22-28, 39-46, 79-83</p>
A	<p>GENESTIER L ET AL: "Caspase-dependent ceramide production in Fas - and HLA class I-mediated peripheral T cell apoptosis." JOURNAL OF BIOLOGICAL CHEMISTRY, (1998 FEB 27) 273 (9) 5060-6. , XP002122830 page 5060, left-hand column, paragraph 2 -right-hand column, paragraph 1 page 5061, left-hand column, paragraph 1 figure 7</p> <p style="text-align: center;">---</p>	<p>1-49, 52-56, 59-83, 138-142</p>
A	<p>SATOH T ET AL: "CHANGES IN MITOCHONDRIAL MEMBRANE POTENTIAL DURING OXIDATIVE STRESS-INDUCED APOPTOSIS IN PC12 CELLS" JOURNAL OF NEUROSCIENCE RESEARCH, US, WILEY-LISS, vol. 50, no. 3, page 413-420 XP002058714 ISSN: 0360-4012 abstract page 413, paragraph 2 -page 414, paragraph 2</p> <p style="text-align: center;">---</p> <p style="text-align: center;">-/--</p>	<p>1-49, 52-56, 59-83, 138-142</p>

INTERNATIONAL SEARCH REPORT

International Application No

PCT/US 99/06874

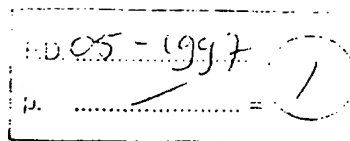
C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT		
Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 98 02579 A (UNIV EMORY) 22 January 1998 (1998-01-22) page 3, line 24 -page 5, line 9 page 13, line 17-20 ----	59-73
A	HERMESH O ET AL: "Mitochondria uncoupling by a long chain fatty acyl analogue." JOURNAL OF BIOLOGICAL CHEMISTRY, (1998 FEB 13) 273 (7) 3937-42. , XP002122831 abstract -----	3,7,25, 46,52

Information on patent family members

PCT/US 99/06874

Form PCT/ISA/210 (patent family annex) (July 1992)

XP-002122832



AN - 97302905 MEDLINE

DN - 97302905

TI - Interferon-gamma enhances susceptibility of cervical cancer cells to lysis by tumor-specific cytotoxic T cells.

AU - Street D; Kaufmann A M; Vaughan A; Fisher S G; Hunter M; Schreckenberger C; Potkul R K; Gissmann L; Qiao L

CS - Department of Obstetrics and Gynecology, Stritch School of Medicine, Loyola University Medical Center, Maywood, Illinois 60153, USA.

SO - GYNECOLOGIC ONCOLOGY, (1997 May) 65 (2) 265-72.

Journal code: FXC. ISSN: 0090-8258.

CY - United States

DT - Journal; Article; (JOURNAL ARTICLE)

LA - English

FS - Priority Journals; Cancer Journals

EM - 199708

EW - 19970802

AB - Recently we have demonstrated that tumor-specific cytotoxic T lymphocytes (CTLs) can be activated by cervical carcinoma cells expressing the costimulatory molecule CD80, which may be used as a therapeutic vaccine for patients with cervical cancer. For activated CTLs to be effective, appropriate amounts of MHC class I expression are required on target tumor cells. In this study, we found that some cervical carcinoma cells expressed only low levels of MHC class I and adhesion molecules such as CD54. We further demonstrated that tumor cells (CaSki and SiHa) expressing low levels of MHC class I were more resistant to lysis by specific CTLs than tumor cells (HeLa) expressing high levels of MHC class I. Treatment of CaSki or SiHa cells with interferon-gamma resulted in an increased expression of MHC class I, MHC class II, and CD54. Expression of CD58 and CD80 was not up-regulated or induced. Treatment of the tumor cells with interferon-gamma significantly enhanced the lysis of the tumor cells by specific CTLs which had been activated by the respective CD80-expressing tumor cells. The enhancement of cytolysis could be blocked by monoclonal antibodies to MHC class I and CD54, but not by that to MHC class II. Furthermore, we found that interferon-gamma induced apoptosis in cervical carcinoma cells but not in tumor-specific CTLs.